# Chromosomal Abnormalities Associated with Omphalocele

Chih-Ping Chen[1,2,3,4]*

*Departments of [1]Obstetrics and Gynecology, and [2]Medical Research, Mackay Memorial Hospital, Taipei, [3]Department of Biotechnology and Bioinformatics, Asia University, Taichung, and [4]College of Chinese Medicine, China Medical University, Taichung, Taiwan.*

## SUMMARY

Fetuses with omphalocele have an increased risk for chromosomal abnormalities. The risk varies with maternal age, gestational age at diagnosis, association with umbilical cord cysts, complexity of associated anomalies, and the contents of omphalocele. There is considerable evidence that genetics contributes to the etiology of omphalocele. This article provides an overview of chromosomal abnormalities associated with omphalocele and a comprehensive review of associated full aneuploidy such as trisomy 18, trisomy 13, triploidy, trisomy 21, 45,X, 47,XXY, and 47,XXX, partial aneuploidy such as dup(3q), dup(11p), inv(11), dup(1q), del(1q), dup(4q), dup(5p), dup(6q), del(9p), dup(15q), dup(17q), Pallister-Killian syndrome with mosaic tetrasomy 12p and Miller-Dieker lissencephaly syndrome with deletion of 17p13.3, and uniparental disomy (UPD) such as UPD 11 and UPD 14. Omphalocele is a prominent marker for chromosomal abnormalities. Perinatal identification of omphalocele should alert chromosomal abnormalities and familial unbalanced translocations, and prompt thorough cytogenetic investigations and genetic counseling. [*Taiwanese J Obstet Gynecol* 2007;46(1):1–8]

**Key Words:** chromosomal abnormalities, genetics, omphalocele

## Introduction

Omphalocele has an incidence of 2–3 per 10,000 live births and is considered to be a heterogeneous condition [1,2]. There is considerable evidence that genetics contributes to the etiology of omphalocele and fetuses with omphalocele have an increased risk for chromosomal abnormalities. The risk varies with maternal age, gestational age at diagnosis, association with umbilical cord cysts, complexity of associated anomalies, and the contents of omphalocele [3–5]. Chromosomal abnormalities have been reported in 10–12% of the neonates with omphalocele and 30% of the fetuses with omphalocele [1,4,6–9]. When the diagnosis is made in early pregnancy, the percentage of aneuploidy can increase to 61.1–66.7% [8,10].

**Correspondence to:* Dr Chih-Ping Chen, Department of Obstetrics and Gynecology, Mackay Memorial Hospital, 92, Section 2, Chung-Shan North Road, Taipei 104, Taiwan.
E-mail: cpc_mmh@yahoo.com
Accepted: February 10, 2007

## Full Aneuploidy

Trisomy 18 and trisomy 13 are the most common chromosomal abnormalities associated with omphalocele (Table 1). Snijders et al [4] found omphaloceles in 22.5% of fetuses with trisomy 18, 9.1% of fetuses with trisomy 13, 12.5% of fetuses with triploidy, and 0.045% of the fetuses without chromosomal abnormalities in a first trimester screening study. Snijders et al [4] also found that the risk for trisomy 18 or trisomy 13 in fetuses with omphalocele at 11–14 gestational weeks was 340 times (17% *vs.* 0.05%) higher than for those without omphalocele. Chen [11] in a study of 89 consecutive cases of fetal trisomy 18 found that 12 cases (13.48%) had omphalocele, and the male to female sex ratio in the fetuses with concomitant omphalocele and trisomy 18 was 2:1.

Snijders et al [8] in a study of 18 fetal omphaloceles diagnosed at 11–14 gestational weeks found that 12 cases (66.7%) had chromosomal abnormalities, of which 10 had trisomy 18, one had trisomy 13, and one had the karyotype of 69,XXX. Blazer et al [10] in a study

**Table 1.** Incidence of chromosomal abnormalities in patients with omphalocele

| Authors | Chromosomal abnormalities/total | Incidence | Gestational weeks at diagnosis* | Chromosomal abnormalities | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | | | | Trisomy 18 | Trisomy 13 | Trisomy 21 | Turner syndrome or 45,X | Triploidy | 47,XXX or 47,XXY | Others |
| Snijders et al [8] | 12/18 | 66.7% | 11–14 | 10 | 1 | – | – | – | 1 | – |
| Blazer et al [10] | 11/18 | 61.1% | 12–16 | 5 | 1 | 2 | 1 | 2 | – | – |
| Calzolari et al [2] | 94/160 | 58.8% | [a] | 60 | 23 | 4 | ? | ? | ? | 7 |
| Gilbert and Nicolaides [12] | 19/35 | 54.3% | 16–36 (23) | 17 | – | – | – | 1 | 1 | – |
| Brantberg et al [5] | 44/90 | 48.9% | 10–39 (18) | 33 | 5 | 1 | 1 | 2 | – | 2 |
| van de Geijn et al [13] | 10/22 | 45.5% | 12–38 (25) | 6 | 1 | – | – | 1 | – | 2 |
| Hughes et al [14] | 13/30 | 43.3% | 12–40 (21) | 4 | 5 | 2 | 1 | – | – | 1 |
| Hwang & Kousseff [15] | 37/93 | 39.8% | [b] | 19 | 2 | 11 | 1 | – | – | 4 |
| Nicolaides et al [6] | 42/116 | 36.2% | 16–39 (21) | 32 | 6 | – | – | 1 | 1 | 2 |
| Goldkrand et al [16] | 9/27 | 33.3% | [c] | 5 | 3 | 1 | – | – | – | – |
| Hauge et al [17] | 12/40 | 30% | [d] | 8 | 2 | 2 | – | – | – | – |
| Stoll et al [18] | 17/58 | 29.3% | [e] | 13 | 3 | 1 | – | – | – | – |
| Snijders et al [4] | 43/153 | 28.1% | 16–26 | 34 | 8 | – | – | 1 | – | – |
| Eydoux et al [19] | 12/46 | 26.1% | 15–36 (26) | 7 | 2 | – | 1 | – | – | 2 |
| Hsu et al [20] | 6/24 | 25% | [f] | 4 | 2 | – | – | – | – | – |
| Getachew et al [3] | 5/22 | 22.7% | 15–34 (24) | 3 | 1 | – | – | – | – | 1 |
| De Veciana et al [21] | 9/40 | 22.5% | 12–39 (21) | 5 | 3 | – | – | – | 1 | – |
| Benacerraf et al [22] | 4/22 | 18.2% | 14–28 | 1 | 2 | – | – | 1 | – | – |
| Chen et al [23] | 4/25 | 16% | 14–38 (26) | 3 | 1 | – | – | – | – | – |
| Salihu et al [24] | 3/26 | 11.5% | [c] | 2 | 1 | – | – | – | – | – |
| St-Vil et al [9] | 9/83 | 10.8% | [g] | 6 | – | 2 | 1 | – | – | – |

**Mean gestational age shown in parentheses; [a]The surveyed population included livebirths, stillbirths, and induced abortions following prenatal diagnosis; [b]Ninety-three karyotyped cases were among 127 cases of omphalocele (74 prenatal cases and 53 pediatric cases); [c]All cases were detected prenatally by ultrasound; [d]Thirty-seven live cases and three stillbirths; [e]Diagnosis was performed prenatally in 61.9% of the cases and the others were diagnosed at birth or in the 1st week of life; [f]Twenty-four karyotyped cases were among 50 infants with omphalocele and an average gestational age of 38.5 weeks at birth; [g]Fifty prenatal cases and 33 pediatric cases.*

of 18 fetal omphaloceles diagnosed at 12–16 gestational weeks found that 11 cases (61.1%) had chromosomal abnormalities, of which five had trisomy 18, two had trisomy 21, two had triploidy, one had trisomy 13, and one had the karyotype of 45,X. Calzolari et al [2] in a study of 160 cases of omphaloceles in 21 regional registers in Europe (EUROCAT registers) found that 94 cases (58.8%) had chromosomal abnormalities, of which 60 had trisomy 18, 23 had trisomy 13, four had trisomy 21, and seven had other chromosomal abnormalities. Gilbert and Nicolaides [12] in a study of 35 fetal omphaloceles found that 19 cases (54.3%) had chromosomal abnormalities, of which 17 had trisomy 18, one had triploidy, and one had the karyotype of 47,XXY. The male to female sex ratio was 3:1. Brantberg et al [5] in a study of 90 prenatally diagnosed omphaloceles found that 44 cases (48.9%) had chromosomal abnormalities, of which 33 had trisomy 18, five had trisomy 13, two had triploidy, one had trisomy 21, one had Turner syndrome, one had the karyotype of mos 47,XY, + 18/92,XXXY, and one had the karyotype of 47,XY, + der(13)t(3;13)(q29;q21.2)mat. The male to female ratio was 1.9:1. The sex ratio was 2.1:1 for central omphalocele and 1.6:1 for epigastric omphalocele. Of interest is that chromosomal abnormalities were found in 40/58 (69%) of the fetuses with central omphalocele and in 4/32 (12.5%) of the fetuses with epigastric omphalocele. van de Geijn et al [13] in a study of 22 fetal omphaloceles found that 10 cases (45.5%) had chromosomal abnormalities, of which six had trisomy 18, one had trisomy 13, one had triploidy, one had 5p+, and one had 8p+. Hughes et al [14] in a study of 30 fetal omphaloceles found that 13 cases (43.3%) had chromosomal abnormalities, of which four had trisomy 18, five had trisomy 13, two had trisomy 21, one had Turner syndrome, and one had del(7q). Hwang and Kousseff [15] in a study of 93 cases of omphalocele found that 37 cases (39.8%) had chromosomal aberrations, of which 19 had trisomy 18, 11 had trisomy 21, two had trisomy 13, one had the karyotype of 45,X, one had the karyotype of mos 46,XX,del(18)(p11)/46,XX,i(18q), one had inv(2)(p11q12)mat, one had inv(3)(p13q11), and one had inv(16)(p11.1q11.2). Nicolaides et al [6] in a study of 116 fetal omphaloceles found that 42 cases (36.2%) had chromosomal abnormalities, of which 32 had trisomy 18, six had trisomy 13, one had the karyotype of 47,XXY, one had triploidy, one had unbalanced t(13;14), and one had del(5p). The male to female sex ratio was 6:1 in the cases with concomitant omphalocele and aneuploidy. Goldkrand et al [16] in a study of 27 cases of fetal omphaloceles found that nine cases (33.3%) had chromosomal abnormalities, of which five had trisomy 18, three had trisomy 13, and one had trisomy 21. Hauge et al [17] in a study of 40 cases of omphaloceles found that 12 cases (30%) had chromosomal abnormalities, of which eight had trisomy 18, two had trisomy 13, and two had trisomy 21. Stoll et al [18] in a study of 58 births with omphaloceles found that 17 cases (29.3%) had chromosomal abnormalities, of which 13 had trisomy 18, three had trisomy 13, and one had trisomy 21. Snijders et al [4] in a study of 153 fetal omphaloceles found that 43 cases (28.1%) had chromosomal abnormalities, of which 34 had trisomy 18, eight had trisomy 13, and one had triploidy. Eydoux et al [19] in a study of 46 fetal omphaloceles found that 12 cases (26.1%) had chromosomal abnormalities, of which seven had trisomy 18, two had trisomy 13, one had the karyotype of 45,X, one had i(18q), and one had a balanced translocation of t(9;11)(p13;q13). Hsu et al [20] in a study of 24 infants with omphaloceles found that six cases (25%) had chromosomal abnormalities, of which four had trisomy 18 and two had trisomy 13. Getachew et al [3] in a study of 22 fetal omphaloceles found that five cases (22.7%) had chromosomal abnormalities, of which three had trisomy 18, one had trisomy 13, and one had inv(11). De Veciana et al [21] in a study of 40 fetal omphaloceles found that nine cases (22.5%) had chromosomal abnormalities, of which five had trisomy 18, three had trisomy 13, and one had the karyotype of 47,XXX. Benacerraf et al [22] in a study of 22 fetal omphaloceles found that four cases (18.2%) had chromosomal abnormalities, of which one had trisomy 18, two had trisomy 13, and one had triploidy. Chen et al [23] in a study of 25 fetal omphaloceles found that four cases (16%) had chromosomal abnormalities, of which three had trisomy 18 and one had trisomy 13. Salihu et al [24] in a study of 24 fetal omphaloceles found that three cases (11.5%) had chromosomal abnormalities, of which two had trisomy 18 and one had trisomy 13. St-Vil et al [9] in a study of 83 neonates with omphalocele found that nine cases (10.8%) had chromosomal abnormalities, of which six had trisomy 18, two had trisomy 21, and one had Turner syndrome.

The association between omphalocele and trisomy 21 is controversial. Torfs et al [25] in an epidemiologic study found only one trisomy 21 infant among 2,979 live births and stillbirths with omphalocele and concluded that trisomy 21 does not predispose the fetus to an increased risk for omphalocele. However, Mastroiacovo et al [26] observed seven cases of trisomy 21 among 8,560 omphaloceles with an incidence of 1/1,200, which is significantly higher than 1/425,000 in the general population and suggested that trisomy 21 does predispose the fetus to an increased risk for

omphalocele. Omphalocele can also be associated with sex chromosome abnormalities such as 45,X, 47,XXY, or 47,XXX [4–6,9,10,12,14,15,19,21,27–29]. Prenatal diagnosis of concomitant cystic hygroma and omphalocele should alert Turner syndrome. Saller et al [27] reported prenatal diagnosis of 45,X in a fetus with omphalocele, cystic hygroma, pleural effusion, and ascites. Govaerts et al [28] reported prenatal diagnosis of 45,X in a fetus with abnormal sonographic findings of omphalocele, cystic hygroma, pleural effusion, ascites, and polyhydramnios at 22 gestational weeks. Goldstein and Drugan [29] reported prenatal diagnosis of cystic hygroma and omphalocele at 11 gestational weeks in a fetus with the karyotype of 45,X. Toriello and Higgins [30] postulated that X-linked midline defects are caused by a single mutation on the X chromosome. Goldstein and Drugan [29] suggested that the occurrence of omphalocele in Turner syndrome may be due to the fact that monosomy X allows expression in early gestation through denial of X-inactivation.

Several reports suggested that chromosomal abnormalities are more common in association with omphaloceles that contain only bowel compared with those that contain only liver [3,14,21,22,31]. For instance, Getachew et al [3] reported aneuploidy in 87% of fetuses with omphalocele and intracorporeal liver compared with 9% of fetuses with omphalocele and extracorporeal liver. Umbilical cord cysts increase the risk of aneuploidy, especially trisomy 18, in fetuses with omphalocele [5,32]. The umbilical cord cysts associated with omphalocele are usually pseudocysts and allantoic cysts [32]. Brantberg et al [5] found that 13 of 90 cases with prenatally diagnosed omphalocele had cysts or pseudocysts of the umbilical cord (12 with central omphalocele and one with epigastric omphalocele). Of the 13 cases with omphalocele and an umbilical cord cyst, 11 (84.6%) had trisomy 18 and two (15.4%) had a normal karyotype.

## Partial Aneuploidy and Uniparental Disomy (UPD)

### *Dup(1q) and del(1q)*

Chen et al [33] reported omphalocele, microphthalmia, coloboma of iris, cerebellar hypoplasia, and bifid thumbs in a male patient with a karyotype of 46,XY,der(21) t(1;21)(q25;q22)pat with dup(1)(q25 → qter) and del(21)(q22 → qter). Rotmensch et al [34] reported the prenatal diagnosis of a female fetus with del(1)(q41 → qter), omphalocele, nuchal webbing, hydrocephalus, cleft palate, and adrenal malformations. The fetus had the karyotype of 46,XX,del(1)(q41) *de novo*.

### *Dup(3q)*

Patients with dup(3q) syndrome usually have duplicated 3q segments within the region of 3q21 → qter and manifest mental and growth retardation, as well as multiple anomalies, some of which overlap with Brachmann-de Lange syndrome, for example, brachycephaly, synophyrys, hirsutism, anteverted nares, downturned corners of the mouth, micrognathia, and high-arched palate [35,36]. The common congenital anomalies associated with 3q duplications are congenital heart defects (septal defects), renal malformations (polycystic kidneys or dysplasia), ocular malformations (strabismus, nystagmus, cataract, corneal opacities, colobomas of the iris, and anophthalmia), and limb anomalies (hypoplasia of the phalanges, camptodactyly, and clinodactyly). Omphalocele can be associated with dup(3q) [37]. The duplications of 3q21 → qter in most patients are the products of unbalanced segregations of balanced parental rearrangements involving other chromosomes and thus present with other chromosome aberrations. The critical region responsible for the typical dup(3q) phenotype is localized to the interval 3q26.3–q27 or 3q26.31–q27.3 [38]. Wilson et al [38] found that 3/13 (23.1%) of the cases with dup(3q) syndrome had omphalocele. Table 2 shows the reported chromosomal rearrangements involving partial trisomy 3q and omphalocele. Allderdice et al [39] reported omphaloceles and partial trisomy 3q (3q21 → qter) in the children of carriers of a pericentric inversion inv(3)(p25q21). Mulcahy et al [40] reported omphalocele and partial trisomy 3q (3q24 → qter) in a 3-month-old infant born to a carrier mother of a pericentric inversion inv(3)(p25q24). Chen et al [36,41,42] reported recurrent omphaloceles in three affected siblings with partial trisomy 3q (3q21 → qter) born to a carrier mother with t(3;11)(q21;q23). Cinti et al [43] reported an abortus with omphalocele and *de novo* partial trisomy 3q (3q24 → qter). Yatsenko et al [44] reported omphalocele and partial trisomy 3q (3q27.3 → qter) in a child of a carrier mother of t(3;4)(q27.3;q32.3). Yatsenko et al [44] further defined the smallest region of overlap (SRO) associated with omphalocele to be between the breakpoint-identifying bacterial artificial chromosome clone and 3qter, and hypothesized that the SRO contains the gene important in normal abdominal wall development.

### *Dup(4q)*

Fryns et al [45] reported Beckwith-Wiedemann syndrome (BWS) with dup(4)(q34.2 → qter) and del(18)(p11.32 → pter) in a 2-month-old girl with omphalocele, a long tongue, birth weight of 3,960 g, microcephaly, wide-spaced and hypoplastic nipples, hypoplastic labia

**Table 2.** Reported cases with chromosomal rearrangements involving partial trisomy 3q and omphalocele

| Authors | Karyotype | Duplicated segment | Deleted segment |
|---|---|---|---|
| Allderdice et al [39] | 46,XY,rec(3)inv(3)(p25q21)pat | 3q21-qter | 3p25-pter |
| | 46,XX,rec(3)inv(3)(p25q21)mat* | 3q21-qter | 3p25-pter |
| | 46,XY,rec(3)inv(3)(p25q21)pat* | 3q21-qter | 3p25-pter |
| | 46,XX,rec(3)inv(3)(p25q21)mat | 3q21-qter | 3p25-pter |
| Mulcahy et al [40] | 46,XX,rec(3)dup(3q)inv(3)(p25q24)mat | 3q24-qter | 3p25-pter |
| Chen et al [36] | 46,XX,der(11)t(3;11)(q21;q23)mat† | 3q21-qter | 11q23-qter |
| Chen et al [41] | 46,XX,der(11)t(3;11)(q21;q23)mat† | 3q21-qter | 11q23-qter |
| Chen et al [42] | 46,XY,der(11)t(3;11)(q21;q23)mat† | 3q21-qter | 11q23-qter |
| Cinti et al [43] | 46,XX,der(20)t(3;20)(q24;p13)*de novo* | 3q24-qter | 20p13-pter |
| Yatsenko et al [44] | 46,XY,der(4)t(3;4)(q27.3;q32.3)mat | 3q27.3-qter | 4q32.3-qter |

**Two affected siblings in the family; †three affected siblings in the family. (Modified from Yatsenko et al [44].)*

majora, and muscular hypertonia as the unbalanced product of paternal t(4;18)(q34.2;p11.32).

### *Dup(5p)*

Schuffenhauer et al [46] reported an interstitial deletion of 5p accompanied by dicentric ring formation of the deleted segment resulting in trisomy 5p13-cen in a 2.5-year-old male with the karyotype of mos 46,XY,del(5)(p10p13)/47,XY,+dic r(5)(p10p13),del(5)(p10p13). The infant manifested omphalocele, macrocephaly, asymmetric square skull, inguinal hernias, hypospadias, and club feet.

### *Dup(6q)*

Stamberg et al [47] reported omphalocele, camptodactyly, club feet, agenesis of the gall bladder, imperforate anus, hydronephrosis, ambiguous external genitalia, and an occipital encephalocele in a male patient with dup(6)(q21 → qter) as an unbalanced product of maternal t(6;22)(q21;p13) or (q21;pter).

### *Del(9p)*

Nagy et al [48] reported omphalocele, trigonocephaly, a prominent forehead, a long philtrum, a small mouth, a high-arched palate, low-set ears, a short neck, widely spaced nipples, long digits, and *de novo* partial monosomy 9p with a deleted segment of 9p22-pter in a female patient with the karyotype of 46,XX,del(9)(p22).

### *Dup(11p), inv(11), and paternal UPD 11*

BWS (OMIM 130650) is characterized by macrosomia, macroglossia, visceromegaly, omphalocele, ear creases/pits, neonatal hypoglycemia, adrenocortical cytomegaly, dysplasia of the renal medulla, and an increased frequency of adrenal carcinoma, nephroblastoma, hepatoblastoma, and rhabdomyosarcoma. The complex modes of inheritance include autosomal dominant inheritance with variable expressivity, contiguous gene duplication at 11p15, genomic imprinting resulting from a defective or absent copy of the maternally derived gene at 11p15, and mutations in the region of chromosome 5q35. About 10–20% of the cases with BWS have paternal UPD 11p15 with a normal karyotype, and about 1% of the cases with BWS have paternal UPD 11p15 with 11p15 duplication [49]. Waziri et al [50] described the association of partial duplication of 11p with BWS. Their first patient with BWS had deletion of 11q23.33-qter and duplication of 11p13-p15, and their second patient had duplication of 11p15. Turleau et al [51] reported trisomy 11p15 in two cases with BWS: one case had *de novo* duplication of 11p15, and the other was the unbalanced product of paternal t(4;11)(q33;p14). Okano et al [52] reported an infant with duplication of the paternal 11pter-p13 segment and BWS. The father was a carrier of a balanced translocation t(4;11)(q35;p13). Slavotinek et al [53] reported paternally inherited duplication of 11p15.5 with BWS in two family members with partial trisomy 11p (11p15.3 → pter) and partial monosomy 5p (5p15.3 → pter) as the unbalanced products of paternal t(5;11)(p15.3;p15.3). Norman et al [54] reported recurrent BWS with inversion of chromosome 11, inv(11)(p11.2p15.5) in two siblings. The phenotypically normal mother carried the same paracentric inv(11) indicating that BWS can be caused by lack of a maternally imprinted gene at 11p15.5. Nystrom et al [55] reported paternal UPD 11 in a case with BWS suggesting that the BWS gene is maternally imprinted [56]. Dutly et al [57] reported a case of BWS with mosaic paternal isodisomy along the whole chromosome 11.

### *Pallister-Killian syndrome (PKS) and mosaic tetrasomy 12p*

PKS (OMIM 601803) is a dysmorphic syndrome characterized by a tissue-limited mosaicism for tetrasomy 12p. PKS has the clinical features of a coarse face, pigmentary

skin anomalies, localized alopecia, profound mental retardation, seizures, relatively frequent occurrence of diaphragmatic defects, and supernumerary nipples. Omphalocele may occasionally be a prenatally identifiable anomaly associated with PKS. Shivashankar et al [58] reported the diagnosis of PKS in a fetus with diminished femoral and humeral lengths, polyhydramnios, and omphalocele on prenatal ultrasound at 24 gestational weeks. Amniocentesis at 31 gestational weeks showed a karyotype of 47,*XY*,+i(12p). Tejada et al [59] reported the prenatal sonographic findings of polyhydramnios, omphalocele, and a short femur length at 26 gestational weeks in a fetus with PKS. The proband postnatally manifested multiple congenital anomalies. The diagnosis of mosaic tetrasomy 12p was confirmed cytogenetically in the cultures of skin fibroblasts and lymphocytes.

### *Paternal UPD 14q*

Towner et al [60] reported perinatal findings of increased nuchal translucency, hydrocephalus, polyhydramnios, a small bell-shaped thorax, large kidneys, hand contractures, short limbs, and omphalocele in a fetus with paternal uniparental isodisomy 14q12-qter. Paternal UPD 14 has been reported to be associated with multiple abnormalities such as thoracic hypoplasia, short and curved ribs, laryngomalacia, ventral wall hernia, kyphosis, short limbs, joint contractures, hypertrophic cardiomyopathy, short stature, craniofacial dysmorphism, and mental retardation [61,62]. Papenhausen et al [63], Cotter et al [64], and Kurosawa et al [61] reported ventral wall hernia associated with paternal UPD 14. Towner et al [60] suggested that prenatal diagnosis of an abdominal wall defect with either increased nuchal translucency or skeletal anomalies should prompt an investigation for UPD 14. Cotter et al [64] suggested that couples with Robertsonian translocations involving chromosome 14 should be counseled the possibility of UPD 14.

### *Dup(15q)*

Lacro et al [65] reported omphalocele with dup(15)(q22.1 → qter) and del(13)(q32.3 → qter). The abortus had the karyotype of 46,XX,der(13)t(13;15)(q32.3;q22.1)mat, omphalocele, a cephalic defect in neural tube closure, and anal atresia.

### *Miller-Dieker lissencephaly syndrome (MDLS) and deletion of 17p13.3*

MDLS (OMIM 247200) is characterized by microcephaly and lissencephaly, a small brain without convolutions or gyri. MDLS is an autosomal dominant disorder caused by deletion of the critical gene on 17p13.3. Reiner et al [66] cloned the gene *LIS-1* (lissencephaly-1) responsible for lissencephaly on 17p13.3. Deletions or mutations in the *LIS-1* gene (OMIM 601545) cause lissencephaly. Omphalocele can be a prenatally identifiable anomaly associated with MDLS [67–69]. Sermer et al [67] reported a case of 17p-associated with prenatally detected omphalocele, cardiomegaly, and neural tube defect. Alvarado et al [68] reported MDLS and omphalocele in a family with multiple affected offspring with del(17)(p13.3 → pter) and the karyotype of 46,*XY*,der(17)t(17;19)(p13.3;q13.33)pat. Chitayat et al [69] reported prenatal diagnosis of omphalocele and mild cerebral ventriculomegaly in a patient with MDLS and the karyotype of 46,*XY*,del(17)(p13.3).

### *Dup(17q)*

Gallien et al [70] reported an infant with omphalocele and dup(17)(q21 → qter). The female infant was the unbalanced product of paternal t(4;17)(p16;q21). The infant had a duplicated segment of 17q21-qter and multiple malformations of coloboma of the iris and microphthalmia, hypoplastic lungs and kidneys, congenital heart defects, omphalocele, Meckel diverticulum, megacolon, hypertrophic labia majora, rudimentary uterus, absent vagina, hypoplastic brain, Dandy-Walker malformation, rhizomelic shortness of limbs, and postaxial hexadactyly of toe phalanges.

## Conclusion

This article provides an overview of chromosomal abnormalities associated with omphalocele. Omphalocele is a prominent marker for chromosomal abnormalities. Perinatal identification of omphalocele should alert chromosomal abnormalities and familial unbalanced translocation, and prompt thorough cytogenetic investigations and genetic counseling.

## References

1. Calzolari E, Volpato S, Bianchi F, et al. Omphalocele and gastroschisis: a collaborative study of five Italian congenital malformation registries. *Teratology* 1993;47:47–55.
2. Calzolari E, Bianchi F, Dolk H, Milan M. Omphalocele and gastroschisis in Europe: a survey of 3 million births 1980–1990. EUROCAT Working Group. *Am J Med Genet* 1995;58:187–94.
3. Getachew MM, Goldstein RB, Edge V, Goldberg JD, Filly RA. Correlation between omphalocele contents and karyotypic abnormalities: sonographic study in 37 cases. *AJR* 1992;158:133–6.
4. Snijders RJM, Sebire NJ, Souka A, Santiago C, Nicolaides KH. Fetal exomphalos and chromosomal defects: relationship

to maternal age and gestation. *Ultrasound Obstet Gynecol* 1995;6:250–5.
5. Brantberg A, Blaas H-GK, Haugen SE, Eik-Nes SH. Characteristics and outcome of 90 cases of fetal omphalocele. *Ultrasound Obstet Gynecol* 2005;26:527–37.
6. Nicolaides KH, Snijders RJ, Cheng H-H, Gosden C. Fetal gastro-intestinal and abdominal wall defects: associated malformations and chromosomal abnormalities. *Fetal Diagn Ther* 1992;7:102–15.
7. Paidas MJ, Crombleholme TM, Robertson FM. Prenatal diagnosis and management of the fetus with an abdominal wall defect. *Semin Perinatol* 1994;18:196–214.
8. Snijders RJM, Brizot ML, Faria M, Nicolaides KH. Fetal exomphalos at 11 to 14 weeks of gestation. *J Ultrasound Med* 1995;14:569–74.
9. St-Vil D, Shaw KS, Lallier M, et al. Chromosomal anomalies in newborns with omphalocele. *J Pediatr Surg* 1996;31:831–4.
10. Blazer S, Zimmer EZ, Gover A, Bronshtein M. Fetal omphalocele detected early in pregnancy: associated anomalies and outcomes. *Radiology* 2004;232:191–5.
11. Chen C-P. Omphalocele and congenital diaphragmatic hernia associated with fetal trisomy 18. *Prenat Diagn* 2005;25:421–3.
12. Gilbert WM, Nicolaides KH. Fetal omphalocele: associated malformations and chromosomal defects. *Obstet Gynecol* 1987;70:633–5.
13. van de Geijn EJ, van Vugt JM, Sollie JE, van Geijn HP. Ultrasonographic diagnosis and perinatal management of fetal abdominal wall defects. *Fetal Diagn Ther* 1991;6:2–10.
14. Hughes MD, Nyberg DA, Mack LA, Pretorius DH. Fetal omphalocele: prenatal US detection of concurrent anomalies and other predictors of outcome. *Radiology* 1989;173:371–6.
15. Hwang P-J, Kousseff BG. Omphalocele and gastroschisis: an 18-year review study. *Genet Med* 2004;6:232–6.
16. Goldkrand JW, Causey TN, Hull EE. The changing face of gastroschisis and omphalocele in southeast Georgia. *J Matern Fetal Neonatal Med* 2004;15:331–5.
17. Hauge M, Bugge M, Nielsen J. Early prenatal diagnosis of omphalocele constitutes indication for amniocentesis. *Lancet* 1983;2(8348):507.
18. Stoll C, Alembik Y, Dott B, Roth MP. Risk factors in congenital abdominal wall defects (omphalocele and gastroschisis): a study in a series of 265 858 consecutive births. *Ann Genet* 2001;44:201–8.
19. Eydoux P, Choiset A, Le Porrier N, et al. Chromosomal prenatal diagnosis: study of 936 cases of intrauterine abnormalities after ultrasound assessment. *Prenat Diagn* 1989;9:255–69.
20. Hsu C-C, Lin S-P, Chen C-H, et al. Omphalocele and gastroschisis in Taiwan. *Eur J Pediatr* 2002;161:552–5.
21. De Veciana M, Major CA, Porto M. Prediction of an abnormal karyotype in fetuses with omphalocele. *Prenat Diagn* 1994;14:487–92.
22. Benacerraf BR, Saltzman DH, Estroff JA, Frigoletto FD Jr. Abnormal karyotype of fetuses with omphalocele: prediction based on omphalocele contents. *Obstet Gynecol* 1990; 75:317–9.
23. Chen C-P, Liu F-F, Jan S-W, Sheu J-C, Huang S-H, Lan C-C. Prenatal diagnosis and perinatal aspects of abdominal wall defects. *Am J Perinatol* 1996;13:355–61.
24. Salihu HM, Boos R, Schmidt W. Omphalocele and gastroschisis. *J Obstet Gynaecol* 2002;22:489–92.
25. Torfs CP, Honoré LH, Curry CJR. Is there an association of Down syndrome and omphalocele? *Am J Med Genet* 1997; 73:400–3.
26. Mastroiacovo P, Robert E, Källén B. Is there an association of Down syndrome and omphalocele? *Am J Med Genet* 1999;82:443.
27. Saller DN Jr, Dailey JV, Doyle DL, Carr SR, Canick JA, Rogers BB. Turner syndrome associated with an omphalocele. *Prenat Diagn* 1993;13:424–6.
28. Govaerts LC, Bongers MY, Lammens MM, Tuerlings JH, van de Kaa CA. Monosomy X and omphalocele. *Prenat Diagn* 1997;17:282.
29. Goldstein I, Drugan A. Cystic hygroma and omphalocele at 11 weeks in a fetus with monosomy X. *Prenat Diagn* 2006; 26:381–2.
30. Toriello HV, Higgins JV. X-linked midline defects. *Am J Med Genet* 1985;21:143–6.
31. Nyberg DA, Fitzsimmons J, Mack LA, et al. Chromosomal abnormalities in fetuses with omphalocele. Significance of omphalocele contents. *J Ultrasound Med* 1989;8:299–308.
32. Chen C-P, Jan S-W, Liu F-F, et al. Prenatal diagnosis of omphalocele associated with umbilical cord cyst. *Acta Obstet Gynecol Scand* 1995;74:832–5.
33. Chen H, Gershanik JJ, Mailhes JB, Sanusi ID. Omphalocele and partial trisomy 1q syndrome. *Hum Genet* 1979;53:1–4.
34. Rotmensch S, Liberati M, Luo JS, Tallini G, Mahoney MJ, Hobbins JC. Prenatal diagnosis of a fetus with terminal deletion of chromosome 1 (q41). *Prenat Diagn* 1991;11:867–73.
35. Steinbach P, Adkins WN Jr, Caspar H, et al. The dup(3q) syndrome: report of eight cases and review of the literature. *Am J Med Genet* 1981;10:159–77.
36. Chen C-P, Jan S-W, Liu F-F, et al. Partial duplication of 3q and distal deletion of 11q in a stillbirth with an omphalocele containing the liver, short limbs, and intrauterine growth retardation. *J Med Genet* 1996;33:615–7.
37. Aqua MS, Rizzu P, Lindsay EA, et al. Duplication 3q syndrome: molecular delineation of the critical region. *Am J Med Genet* 1995;55:33–7.
38. Wilson GN, Dasouki M, Barr M Jr. Further delineation of the dup(3q) syndrome. *Am J Med Genet* 1985;22:117–23.
39. Allderdice PW, Browne N, Murphy DP. Chromosome 3 duplication q21 → qter deletion p25 → pter syndrome in children of carriers of a pericentric inversion inv(3)(p25q21). *Am J Hum Genet* 1975;27:699–718.
40. Mulcahy MT, Pemberton PJ, Sprague P. Trisomy 3q: two clinically similar but cytogenetically different cases. *Ann Genet* 1979;22:217–20.
41. Chen C-P, Lee C-C, Chuang CY, et al. Recurrent omphalocele with partial trisomy 3q and partial monosomy 11q. *Clin Genet* 1997;52:196–8.
42. Chen C-P. Inconsistency of omphalocele contents in three consecutive siblings with partial trisomy 3q and partial monosomy 11q. *Prenat Diagn* 1999;19:591.
43. Cinti R, Botta G, Asnaghi V, Del Monaco A, Salvego M, Silengo M. *De novo* partial duplication of 3q and distal deletion of 20p in a 15-week abortus with omphalocele. *Fetal Diagn Ther* 2000;15:61–2.
44. Yatsenko SA, Mendoza-Londono R, Belmont JW, Shaffer LG. Omphalocele in trisomy 3q: further delineation of phenotype. *Clin Genet* 2003;64:404–13.

45. Fryns JP, Kleczkowska A, Devriendt K, Devliegher H, Van den Berghe H. Wiedemann-Beckwith syndrome and chromosomal duplication 4q/deficiency 18p. *Genet Counsel* 1993;4:37–41.
46. Schuffenhauer S, Kobelt A, Daumer-Haas C, et al. Interstitial deletion 5p accompanied by dicentric ring formation of the deleted segment resulting in trisomy 5p13-cen. *Am J Med Genet* 1996;65:56–9.
47. Stamberg J, Shapiro J, Valle D, Kuhajda FP, Thomas G, Wissow L. Partial trisomy 6q, due to balanced maternal translocation (6;22) (q21; p13) or (q21; pter). *Clin Genet* 1981;19:122–5.
48. Nagy E, Bod M, Nemeth I, Timar L. Short clinical report: a new case with *de novo* partial 9p monosomy. *Acta Paediatr Hung* 1991;31:407–13.
49. Weksberg R, Smith AC, Squire J, Sadowski P. Beckwith-Wiedemann syndrome demonstrates a role for epigenetic control of normal development. *Hum Mol Genet* 2003;12(Spec No. 1):R61–8.
50. Waziri M, Patil SR, Hanson JW, Bartley JA. Abnormality of chromosome 11 in patients with features of Beckwith-Wiedemann syndrome. *J Pediatr* 1983;102:873–6.
51. Turleau C, de Grouchy J, Chavin-Colin F, Martelli H, Voyer M, Charlas R. Trisomy 11p15 and Beckwith-Wiedemann syndrome. A report of two cases. *Hum Genet* 1984;67:219–21.
52. Okano Y, Osasa Y, Yamamoto H, Hase Y, Tsuruhara T, Fujita H. An infant with Beckwith-Wiedemann syndrome and chromosomal duplication 11p13 → pter: correlation of symptoms between 11p trisomy and Beckwith-Wiedemann syndrome. *Jpn J Hum Genet* 1986;31:365–72.
53. Slavotinek A, Gaunt L, Donnai D. Paternally inherited duplications of 11p15.5 and Beckwith-Wiedemann syndrome. *J Med Genet* 1997;34:819–26.
54. Norman AM, Read AP, Clayton-Smith J, Andrews T, Donnai D. Recurrent Wiedemann-Beckwith syndrome with inversion of chromosome (11)(p11.2p15.5). *Am J Med Genet* 1992;42:638–41.
55. Nystrom A, Cheetham JE, Engstrom W, Schofield PN. Molecular analysis of patients with Wiedemann-Beckwith syndrome. II. Paternally derived disomies of chromosome 11. *Eur J Pediatr* 1992;151:511–4.
56. Schinzel A. Genomic imprinting: consequences of uniparental disomy for human disease. *Am J Med Genet* 1993;46:683–4.
57. Dutly F, Baumer A, Kayserili H, et al. Seven cases of Wiedemann-Beckwith syndrome, including the first reported case of mosaic paternal isodisomy along the whole chromosome 11. *Am J Med Genet* 1998;79:347–53.
58. Shivashankar L, Whitney E, Colmorgen G, et al. Prenatal diagnosis of tetrasomy 47,XY,+i(12p) confirmed by *in situ* hybridization. *Prenat Diagn* 1988;8:85–91.
59. Tejada MI, Uribarren A, Briones P, Vilaseca MA. A further prenatal diagnosis of mosaic tetrasomy 12p (Pallister-Killian syndrome). *Prenat Diagn* 1992;12:529–34.
60. Towner D, Yang SP, Shaffer LG. Prenatal ultrasound findings in a fetus with paternal uniparental disomy 14q12-qter. *Ultrasound Obstet Gynecol* 2001;18:268–71.
61. Kurosawa K, Sasaki H, Sato Y, et al. Paternal UPD 14 is responsible for a distinctive malformation complex. *Am J Med Genet* 2002;110:268–72.
62. Kotzot D, Utermann G. Uniparental disomy (UPD) other than 15: phenotypes and bibliography updated. *Am J Med Genet* 2005;136A:287–305.
63. Papenhausen PR, Mueller OT, Johnson VP, Sutcliffe M, Diamond TM, Kousseff BG. Uniparental isodisomy of chromosome 14 in two cases: an abnormal child and a normal adult. *Am J Med Genet* 1995;59:271–5.
64. Cotter PD, Kaffe S, McCurdy LD, Jhaveri M, Willner JP, Hirschhorn K. Paternal uniparental disomy for chromosome 14: a case report and review. *Am J Med Genet* 1997;70:74–9.
65. Lacro RV, Jones KL, Mascarello JT, Jones OW, Wilson N, Jones MC. Duplication of distal 15q: report of five new cases from two different translocation kindreds. *Am J Med Genet* 1987;26:719–28.
66. Reiner O, Carrozzo R, Shen Y, et al. Isolation of a Miller-Dieker lissencephaly gene containing G protein beta-subunit-like repeats. *Nature* 1993;364:717–21.
67. Sermer M, Benzie RJ, Pitson L, Carr M, Skidmore M. Prenatal diagnosis and management of congenital defects of the anterior abdominal wall. *Am J Obstet Gynecol* 1987;156:308–12.
68. Alvarado M, Bass HN, Caldwell S, Jamehdor M, Miller AA, Jacob P. Miller-Dieker syndrome. Detection of a cryptic chromosome translocation using *in situ* hybridization in a family with multiple affected offspring. *Am J Dis Child* 1993;147:1291–4.
69. Chitayat D, Toi A, Babul R, et al. Omphalocele in Miller-Dieker syndrome: expanding the phenotype. *Am J Med Genet* 1997;69:293–8.
70. Gallien JU, Neu RL, Wynn RJ, Steinberg-Warren N, Bannerman RM. An infant with duplication of 17q21 lead to 17qter. *Am J Med Genet* 1981;8:111–5.